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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,035	02/09/2001	Tariq Ghayer	BBC-084	8433

7590 10/26/2007

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
10/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/780,035	GHAYER ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-12 and 14-61* is/are pending in the application.

4a) Of the above claim(s) *39-43 and 47-60* is/are withdrawn from consideration.

5)☒ Claim(s) *37 and 38* is/are allowed.

6)☒ Claim(s) *5- 12, 14-36, 44-46 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission, filed on 3/12/07, has been entered.

As indicated in the Advisory Action, mailed 10/24/06,
Applicant's amendment, filed 10/11/06 has been entered.

Claims 5-12 and 14-61 are pending.

Claims 5- 12, 14-38, 44-46 and 61 are under consideration in the instant application.

Claims 39-43, and 47-60 have been withdrawn as being drawn to the non-elected invention.

Claims 1-4 and 13 have been canceled previously.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.

This Action will be in response to applicant's amendments/arguments, filed 10/24/06.
The rejections of record can be found in the previous Office Actions.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

See the previous Office Actions for a more detailed analysis of applicant's arguments.

3. As indicated in the Advisory Action, mailed 10/24/06,
the previous rejections under 35 USC 112, first paragraph, new matter, written description and enablement were withdrawn in view of applicant's amendment and amended claims, filed 10/11/06, which recited antibodies comprising both a heavy chain variable region and a light chain variable region.

However, upon a review of the instant claims, New Grounds of Rejection have been set forth herein to address the recitation of modifying the claimed antibodies with "at least one amino acid substitution".

4. This is a New Grounds of Rejection.

Claims 6-10, 12, 16-21 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6-10, 12, 16-21 and 24 are indefinite are indefinite in the recitation of "IL-18 activity" and "neutralizing antibody" because the metes and bounds of "IL-18 activity" and the "neutralizing antibody" are ill-defined and ambiguous. "IL-18 activity" and "neutralizing antibody" are not defined by the claims and the specification does not provide a standard for ascertaining the requisite degree or direction and, in turn, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention or the parameters by which to determine said metes and bounds .

It is suggested to amend the claim to recite the particular characteristics of "IL-18 activity" and neutralizing antibody" intended, including the parameters and direction of such "activity" or "neutralizing", by setting forth testable functions, provided there is written description in the specification as filed.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 23-27 and 32-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It has been well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having

antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al. (PNAS 79: 1979-1983, 1982). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Panka et al. (PNAS 85: 3080-3084, 1988) demonstrated that a single amino acid substitution of serine for alanine results in decreased affinity.

In turn, it would have been unpredictable that the anti-CD18 antibodies as defined by the claims which contain "at least one amino acid modification such as a substitution or insertion" of an anti-IL-18 antibody would have the required binding function as well as those "that improve neutralization of IL-18".

The specification does not provide sufficient direction or guidance regarding how to produce anti-CD18 antibodies with any modification, such as any substitution or insertion of any amino acid, as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Without sufficient guidance, it would require undue experimentation of the skilled artisan to make antibodies or antigen-binding fragments thereof which could bind IL-18 and be used in methods of inhibiting IL-18 function that comprised fewer than all six CDRs from a parental antibody that bound IL-18.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Given the recognized unpredictable nature of making antibodies with a desired specificity having any modification, such as any substitution or insertion, from a reference antibody and the lack of sufficient guidance provided in the specification; the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 4-12, 14-24, 44-46 and 61 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kucherlapati et al. (US Patent No. 6,075,181, of record) and Dinarello et al. (J. Leukoc. Biol. 1998, 63:658-664. IDS #A4), for the reasons of record set forth in the previous Office Actions.

Applicant's arguments, in conjunction with basic legal principles of obviousness, filed 10/24/06, have been fully considered, but are not deemed persuasive for reasons or record set forth in the previous Office Actions and reiterated herein, in part, for applicant's convenience.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

See the previous Office Actions for a more detailed analysis of applicant's arguments.

Again, applicant had continued to argue that Dinarello does not teach, suggest or motivate to generate fully human antibodies to IL-18, that Kucherlapati does not disclose IL-18, and does not teach, suggest or motivate to generate fully human antibodies to either IL-18, or specifically to human IL-18, that cited references, either singularly or in combination, do not teach, suggest or motivate the same, or method of making the same, and that the examiner fails to provide any evidence to support motivation to combine the cited art, and merely showing that all the elements of the claimed invention are known in the art is insufficient to establish obviousness.

Again, as pointed out previously, this argument has not been found persuasive for the following reasons.

Again, in response to applicant's continual argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, the teaching, suggestion, or motivation to make the claimed antibody can be readily found in the cited references as Dinarello teaches availability of human IL-18, the involvement of IL-18 in clinical pathology as that antibodies to IL-18 can inhibit the in vivo production of other pro-inflammatory cytokines, and that neutralizing anti-IL-I8 antibodies are a therapeutic option for specific blockade of IL-18.

Additionally, Kucherlapati teaches a method of producing fully human monoclonal antibodies to any protein of interest, but especially cytokines, and advantages of such antibodies in avoiding the undesired immune responses elicited by administering non-human antibodies to humans. Therefore, it is instantly obvious to a person having ordinary skill in the art to combine the teachings of the cited references and to make the human anti-IL-18 antibodies as claimed for the purpose of disease treatment using the method taught by Kucherlapati.

Again, applicant has continued to argue that without applicants disclosure, it is not obvious to make a leap from various therapeutic options as clinical strategy to block IL-18 to one specific cure, namely a human anti-IL-18 antibody, or to combine the teachings of the two references to arrive at applicants invention.

Again, this argument has not been found persuasive because none of the teachings, from which the instant rejection relies upon, is from applicants disclosure, instead they are all from the cited prior art references.

Again, applicant has argued in conjunction with Cardiac Pacemakers Inc. v. St. Jude Medical, Inc. 381 F.3d 1371, 1377 (2004), that recognition of a need does not render obvious the achievement that meets that need, and there is an important distinction between the general motivation to cure an uncured disease and the motivation to create a particular cure, that none of the cited art singularly or in combination, provides any teaching, suggestion, or motivation to arrive at applicants invention, and that a disclosure of a method to generate human monoclonal antibodies, combined with a reference disclosing neutralizing anti-IL-18 antibodies is not a clear and particular teaching, suggestion, or motivation to make the fully human anti-IL-18 antibody of the present invention.

Again, this argument has not been persuasive for the following reasons. First, if either reference had explicitly taught the antibody as claimed, the present invention would have been rejected under 35 U.S.C. 102. Further, besides the reasons addressed above, the cited case law does not apply in the instant situation because in addition to the teachings of neutralizing anti-IL-18 antibodies, more importantly, Dinarello clearly teaches 1) the pathological role of IL-18 in disease development as that IL-18 is evolving as a major as a pro-inflammatory cytokine with implications for a role in inflammatory and infectious diseases, and it may also be a player in autoimmune diseases (page 658, the right column), and anti-IL-I8 antibodies suitable for treating human diseases, and 2) neutralizing anti-IL-I8 antibodies are a therapeutic option for specific blockade of IL-18. Furthermore, though Dinarello does not teach a human anti-IL-18 antibody or a method of making such, Kucherlapati teaches a method of producing fully human monoclonal antibodies to any protein of interest, but especially cytokines, and advantages of such antibodies.

Therefore in contrast to applicant's assertions, the combined teachings provide strong teaching, suggestion, or motivation to arrive at applicant's invention.

Again, applicant has argued that the combination of the cited art is made by the examiner, upon guidance, direction, and motivation to do so, by applicant's present invention, and that this is hindsight reconstruction and is impermissible as a basis for 103 rejection.

Again, this argument has not been found persuasive for the reasons addressed above. In addition, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Also, the arguments of counsel cannot take the place of objective evidence in the record. In re Schulze, 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(c).

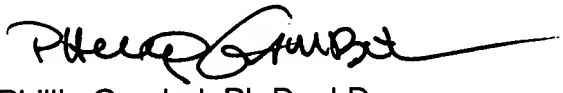
Applicant's arguments have not been found persuasive.

9. Claims 37 and 38 are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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March 29, 2007